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10/553,462	05/05/2006	Makrina Savvidou	HO-P03236US0	8934

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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
12/09/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/553,462	SAVVIDOU ET AL.	
	Examiner	Art Unit	
	ANOOP SINGH	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-8 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6-8 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendments and arguments filed September 22, 2010 has been received and entered. Claims 1, 6-8 and 11 are pending.

Election/Restrictions

Applicant's election without traverse of claims 1-2 and 4-11 in the reply filed on August 31, 2007 was acknowledged.

Claims 1, 6-8 and 11 are under consideration.

Maintained -Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 6-7 and 8 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Holden et al (Am J Obstet Gynecol. 1998; 178(3):551-6, art of record), Ellis et al (Acta Obstr. Gynecol Scand 2001, 80, 602-608, IDS) and Boger (WO 2002/14873, 2/21/2002, IDS) for the reasons of record.

Claims are directed a method of determining that a pregnant woman is at risk of developing pre-eclampsia or that her fetus is at risk of developing intrauterine growth restriction (IUGR), which method comprises: (a) measuring asymmetric dimethylarginine (ADMA) in a plasma sample taken from a pregnant woman at a stage of pregnancy from 23 to 25 weeks gestation; and (b) determining that the woman is at risk of developing pre-eclampsia or her fetus is at risk of developing IUGR if the level of ADMA in the plasma sample is greater than 1.5 gmol/L. Claim 6 limits the method of claims 1, wherein determining that the woman is at risk of developing pre-eclampsia or determining that her fetus is at risk of developing IUGR comprises determining that the woman's ADMA level is at least 3 times the normal pregnancy level.

Holden et al teach a method comprising (a) measuring asymmetric dimethylarginine (ADMA) in a plasma sample taken from a pregnant woman at different stage of pregnancy; and (b) determining the level of ADMA in the plasma sample. It is noted that Holden et al also

determined the level of ADMA to be around 0.52 μmol/L to 1.17 μmol/L during second trimester. This would meet the claim limitation of measuring pregnancy at different stage of pregnancy (including 23-25 weeks) that is embraced by the teaching of Holden (see page 553, Figure 1 B). It is further disclosed that pregnant woman have pre-eclampsia if ADMA in the plasma sample is 1.25 gmol/L (see figure 1A). Therefore, any ADMA level greater than 0.75 μmol/L would also have PE meeting the limitation of the claim. It is further noted that Holden et al conclude that during later stage of pregnancy circulating concentrations increase and, when pregnancy is complicated by preeclampsia. Thus, method of Holden is primarily directed to study the role for ADMA in the changes in blood pressure seen in both normal and preeclampsia pregnancy (see abstract and page 555, col. 1, para. 4). While Holden et al teach a method of (a) measuring ADMA level at least in pregnant women and reported (d) determining that woman has pre-eclampsia if ADMA in the plasma sample is greater than1.17 gmol/L, but differ from claimed invention by not measuring the ADMA level in women at 23 to 25 weeks gestation.

However, such was disclosed by Ellis et al, teach a method comprising (a) measuring asymmetric dimethylarginine (ADMA) in a plasma sample taken from a pregnant woman at different stage of pregnancy including 24-32 weeks gestation; and (b) determining the level of ADMA in the plasma sample (limitation of claim 1). It is disclosed that plasma concentrations of asymmetric dimethylarginine (ADMA) are significantly elevated both in mild preeclampsia during pregnancy from 24 to 32 weeks gestation that includes 24 and 25 weeks gestation (see abstract, figure 1 and 2). It is relevant to point out that Ellis teaches measuring ADMA level in plasma of pregnant woman at stage 24-25 weeks gestation and reported that pregnant woman have pre-eclampsia if ADMA in the plasma sample is greater than 0.75μmol/L (see figure 1), which is significantly higher than normal level ($p<0.04$) (see figure 1). Ellis et al further contemplate studying ADMA and SDMA level early in the pregnancy in order to ascertain if levels rise early enough to predict preeclampsia (see page 607, col. 1, para. 1). While Ellis et al teach a method of measuring ADMA level in women at 24 to 32 weeks gestation having preeclampsia, but differ from claimed invention by not measuring the ADMA level in non pre screened pregnant women.

Boger et al cure the deficiency by teaching a method of detecting the risk of developing a disease including pre-eclampsia that is associated with NO metabolism by (a) measuring the level of ADMA and SDMA (see claims 1 and 9). Boger et al also disclose that preeclampsia is a disease of the NO metabolism leads to constriction of arteries which induces high blood pressure in the mother and poses a risk to the unborn child due to reduced placental perfusion (see page 2) With respect to claim 7 and 8, Boger et al contemplate measuring the ratio of ADMA to SDMA in the plasma of the patient (see claim 14, 20 and 21). It is also disclosed that subject suffering from chronic conditions (CHF, example 4) show ADMA concentration of 4.1 μM/L as compared to 1.0 μM/L in normal subject.

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the method of Holden of measuring the ADMA level in detecting the risk of developing a disease including pre-eclampsia in the mother due to reduced placental perfusion as disclosed by Boger using the known method disclosed by Holden and Ellis. It would have been *prima facie* obvious to one of ordinary skill in the art to combine the known methods of Holden, Ellis and Boger to measure the ADMA level in a pregnant women at a stage of pregnancy comprising 23-25 and determine the level of ADMA to detect the risk of developing of pre-eclampsia

particularly since both Holden and Ellis generally embraced the potential of measuring ADMA level to determine the risk of developing pre-eclampsia. Other limitations of measuring ADMA level that is at least 3 times or ADMA/SDMA level 5 times than the normal pregnancy level would be implicit in the method taught by the combination of references and therefore would be obvious variables when measuring the level of ADMA or SDMA in pregnant women predisposed to develop PE as disclosed by Ellis. One who would have practiced the invention would have had reasonable expectation of success since Ellis and Holden both taught method to measure ADMA level in the plasma of subject to determine if the subject is at risk of developing PE, while combining the teaching Holden, Ellis with Boger would have resulted in a determining that woman is at risk of developing PE if the ADMA level is greater then normal control as suggested by Ellis.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claims 1 and 11 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Holden et al (Am J Obstet Gynecol. 1998; 178(3):551-6, art of record), Ellis et al (Acta. Obstr. Gynecol. Scand. 2001: 80, 602-608, IDS) and Boger (WO 2002/14873, 2/21/2002, IDS) as applied to claims 1, 6-8 above, and further in view of Albaiges et al (Obstet Gynecol 2000;96:559-64, IDS) for the reasons of record.

The teachings of Holden et al, Ellis et al and Boger were described above and relied in same manner here. The combination of art teach a method of determining that a pregnant woman is at risk of developing pre-eclampsia or that her fetus is at risk of developing intrauterine growth restriction (IUGR), which method comprises measuring asymmetric dimethylarginine (ADMA) in a plasma sample taken from a pregnant woman at a stage of pregnancy from 23 to 25 weeks gestation, but differ from claimed invention by not disclosing use of Doppler waveform analysis of uterine arteries and/or flow mediated dilatation of the brachial artery in the women.

However, use of Doppler wave form to predict PE in pregnant women was known and routinely used by one of ordinary skill in the art. For instance, Albaiges et al discloses color doppler of uterine artery imaging of women with singleton pregnancies at 23 weeks to determine bilateral uterine artery notches, left and right uterine artery pulsatility indices (PI) for predicting preeclampsia and delivery of small-for-gestational-age infants (See abstract).

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art seeking to predict risk of developing PE would combine the respective teachings of Holden et al, Ellis et al and Boger by modifying the method to further to further include Doppler waveform analysis of uterine arteries to determine if a pregnant woman is at risk of developing PE as disclosed by Albaiges et al, with a reasonable expectation of success. A person of skill in the art would have been motivated to modify the method by further conducting Doppler analysis as disclosed by Albaiges et al, as a matter of design choice, said design choice amounting to combining prior art method directed to diagnose same condition (PE) according to known methods to yield predictable results. One of ordinary skill in the art would be motivated to use color Doppler for diagnosis of PE because Albaiges et al teaches successful use of color doppler

of uterine artery imaging of women with singleton pregnancies at 23 weeks predict preeclampsia in women risk of developing PE (supra) . One of skill in the art would have been expected to have a reasonable expectation of success in determining if a pregnant woman is at risk of developing pre-eclampsia or IUGR by measuring ADMA and color Doppler imaging because the art teaches the successful diagnosis of PE by measuring plasma ADMA and use of Doppler waveform analysis of uterine arteries. It should be noted that the *KSR* case forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR*, 82 USPQ2d at 1396) (available at http: www. uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf).

Response to arguments

Applicants disagree with the rejection of claim 1 over Holden et al in view of Ellis and Boger, arguing that Holden describes ADMA levels of pre-eclamptic patients during the third trimester that is outside of the 23-25 week. Applicant assert that a a measurement 1.17 mmol/L at 23-25 weeks would not trigger a determination that a woman is at risk of developing pre-eclampsia or that her fetus is at risk of developing IUGR. Applicants further argue that Ellis describes testing patients to determine ADMA levels at a stage of pregnancy of 24-32 weeks. The range of ADMA levels of pre-eclamptic patients was determined to be in the range of 0.4-.1 µmol.L). Applicant assert that Ellis does not disclose an ADMA level of greater than 1.5 µmol/L. Applicants argue that the levels observed by Ellis are lower than the level of 1.17 µmol/L observed by Holden (see page 4, para. 3-4 of the arguments). Applicants further argue that Boger do not cure the deficiency and thus conclude that none of the references suggests that a level of 1.5 µmol/L or greater at a stage of pregnancy from 23 to 25 weeks would be indicative of preeclampsia. Applicants' arguments have been fully considered, but are not found persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants have further engaged in selective reading of the teachings of Holden et al in view of Ellis. to formulate the grounds for teaching away. It should be noted that the ultimate goal of measuring ADMA level in plasma of a pregnant woman is to suggest that a changes in the circulating concentration of ADMA is

important in the pathophysiologic mechanisms of preeclampsia through a reduction in nitric oxide synthesis (see Holden et al, page 552, col. 1, last para).

As previously indicated, Holden et al in describing method disclose (a) measuring asymmetric dimethylarginine (ADMA) in a plasma sample taken from a pregnant woman at different stage of pregnancy, and (b) determining the level of ADMA in the plasma sample. It is noted that Holden et al also determined the level of ADMA to be around 0.52 μmol/L to 1.17 μmol/L during second trimester (supra), but differ from claimed invention by not measuring the ADMA level in women at 23 to 25 weeks gestation. However, measuring level of plasma ADMA in pregnant woman at 24-34 weeks of gestation and determining if the subject woman has higher level of ADMA (>0.8μmol/L, Fig. 1 Ellis) suggesting risk of mild pre-eclampsia was known (see Ellis et al Figure 1). In view of foregoing teachings in prior art, one of ordinary skill in the art would conclude that a higher plasma level of ADMA ((>0.8μmol/L, Fig. 1 Ellis) in a pregnant woman (24-32weeks gestation) would put the woman at risk of developing pre-eclampsia. To the extent that Ellis. describe the measuring ADMA level in a plasma taken from a pregnant woman at a stage 24-34 weeks gestation and determining that woman is risk of developing PE if ADMA level is greater than 0.8, the rejection is applicable to the instant case. Applicants' selective reading of Holden et al. ignores the teachings of the reference of Ellis. There is no requirement for Holden et al. to teach that which is clearly taught by Ellis et al. It should be noted that determining that the woman is at risk of developing mild PE if the plasma level greater that 0.8μmol/l as exemplified in Ellis would necessarily mean that ADMA level any higher than 0.8μmol/L such as 1.5 μmol/L must also put the woman at risk of developing pre-eclampsia (PE) (emphasis added).

Applicant should further note that prior art summarized by the reference of Boger et al is applied to the extent it teaches method of detecting the risk of developing a disease including pre-eclampsia that is associated with NO metabolism by (a) measuring the level of ADMA and SDMA (see claims 1 and 9). Boger et al also disclose that preeclampsia is a disease of the NO metabolism leads to constriction of arteries which induces high blood pressure in the mother and poses a risk to the unborn child due to reduced placental perfusion (see page 2) It is also disclosed that subject suffering from chronic conditions (CHF, example 4) show ADMA

concentration of 4.1 μM/L as compared to 1.0 μM/L in normal subject. Therefore, it is apparent from the teaching of Boger that higher level of ADAM could also determined if the pregnant woman has underlying cardiac or other conditions (CHF, smoking and obesity) that are known to further increase plasma ADMA level. Thus, contrary to applicants' arguments plasma ADMA level in the pregnant woman could vary depending upon various under lying conditions that are known in prior art. To the extent prior art teaches determining plasma level greater than 0.8μmol/liter predisposes woman of developing PE, it must necessarily mean that an ADMA level any higher than 0.8μmol/L such as 1.5 μmol/Las claimed in the instant application must also put the woman at risk of developing PE. Therefore, teaching of Holden, Ellis and Boger would be been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Therefore, in view of the fact patterns of the instant case, and the ground of rejection outlined by the examiner, applicants' arguments are not compelling and do not overcome the rejection of record.

On pages 5, last para and page 5 , first para of the arguments, Applicant re-iterates and rely on their previous arguments that have been discussed in preceding section . The arguments are substantially the same as those addressed in the foregoing response.

Should applicants provide evidence pertinent to secondary consideration to obviousness relating to criticality of five times or more ADMA/SDMA level in a pregnant woman at a stage 23 to 25 weeks gestation predisposes said woman to PE, instant obviousness may be overcome, pending further consideration.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Anoop Singh/
Examiner, Art Unit 1632